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Effects of anti-TNF therapy and immunomodulators on anxiety and depressive symptoms in patients with inflammatory bowel disease: a 5-year analysis

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Abstract

Background and aims: Anxiety and depression are prevalent in patients with inflammatory bowel diseases (IBD), especially during IBD flares. IBD therapies can profoundly affect the mood of patients with IBD. We aimed to determine the long-term impact of anti-tumor necrosis factor (anti-TNF) and immunomodulators (IM) on anxiety and depressive symptoms in IBD patients.

Methods: We compared three treatment groups with IM only (group A), anti-TNF ± IM (group B) and no such therapy (group C). Patients completed the hospital anxiety and depression scale (HADS) at 1 year, 3 years, and 5 years after start of treatment.

Results: In total, 581 patients with IBD (42.9% Crohn's disease, 57.1% ulcerative colitis/IBD unclassified) participated in this study. Effects of treatment were analyzed in a mixed effects model, with and without correction for confounders. Compared with group C, group B showed

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a significant treatment-related improvement in both anxiety and depressive symptoms within the first 2.5 years and also thereafter. Group A showed a significant long-term improvement of anxiety and both short-term and long-term improvement in depressive symptoms. The significance of these results was maintained after correction for confounders, including corticosteroid treatment. Additionally, both groups A and B showed a significant decrease in disease activity in the first 2.5 years after start of treatment and also thereafter. Anti-TNF and IM treatment were associated with a similarly significant decrease in anxiety and depressive symptoms over an observation period of up to 5 years.

Conclusion: Besides a clear benefit for disease activity, anti-TNF and IM apparently improve the mood of patients with IBD.

Keywords: anti-TNF, anxiety, depressive symptoms, hospital anxiety and depression scale, immune-modulatory therapy, inflammatory bowel disease, mood, psychosocial factors

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Introduction

Inflammatory bowel disease (IBD) refers to a chronic relapsing inflammatory condition with the main subtypes ulcerative colitis (UC), IBD unclassified (IBDU) and Crohn's disease (CD). Besides gastrointestinal symptoms, IBD is associated with a clinically relevant psychosocial burden,[1–6] with up to three times higher rates of depressive symptoms and anxiety in IBD patients compared with the general population.[5,7–9]

In IBD patients with moderate-to-severe disease activity, treatment with anti-tumor necrosis factor (anti-TNF) blocking agents, immunomodulators (IM) or systemic corticosteroids is recommended.[10] While systemic corticosteroids can trigger depressive symptoms and anxiety, this medication can also improve patient mood.[6,11,12] Specifically, symptoms of depression and anxiety improved under therapy with anti-TNF therapy in patients with different chronic conditions, including inflammatory diseases.[13–16] One study suggested that a reduction in depression in patients with IBD treated with infliximab for 4 weeks could be due to an improvement of disease activity.[6]

Depressive symptoms and anxiety are about twice as frequent in IBD patients with active *versus* inactive disease,[17] yet this relationship has been discussed controversially,[18] with no causal link established to date.[19–22] On the other hand, symptoms of depression and anxiety have been linked to more severe IBD symptoms, increased hospitalization rates,[23] and lower adherence to treatment,[24] including anti-TNF therapy.[25] Data from the Swiss-IBD cohort study (SIBDCS) showed a significant association between depressive symptoms and anxiety with clinical recurrence over time for all patients with IBD,[26] in agreement with other studies.[4] However, the complexity of the interplay of anti-TNF treatment with mood and the disease course has not yet been disentangled.

Using SIBDCS data, we analyzed the effects of anti-TNF therapy on depressive symptoms and anxiety during the course of IBD in patients with flares and quiescent disease. We hypothesized that treatment with anti-TNF ± immuno-modulatory therapy would result in clinically relevant changes in anxiety and depressive symptoms when compared with immunomodulatory therapy only or none of these therapies. We further hypothesized that these effects would remain robust in a fully corrected multivariable analysis.

Methods

Study design and population

We analyzed prospectively data obtained from the SIBDCS, a nationwide registry, which started enrollment of IBD patients in 2006. For the longitudinal analysis, we considered all patients who were enrolled into SIBDCS between 2006 and 2018. We compared three treatment groups: group A (immuno-modulatory therapy only for at least 2.5 years), group B (anti-TNF therapy ± immuno-modulatory therapy for at least 2.5 years), group C (no anti-TNFs, no immuno-modulatory therapy and follow up of at least 2.5 years). Immunomodulatory therapy was defined as either azathioprine, 6-mercaptopurine,

or methotrexate. Anti-TNF therapy was defined as either infliximab, adalimumab, certolizumab pegol, or golimumab. Local or systemic steroid treatment was allowed in all groups (A–C) and steroid used was assessed across groups A–C.

Only patients who filled the psychosocial questionnaire: (a) before therapy (groups A, B) or within 180 days after enrollment (group C), (b) for a second measurement between 180 and 540 days after having started the therapy (groups A, B) or enrollment (group C), and (c) for a third measurement at least one more time more than 900 days and/or for a fourth measurement more than 1600 days after start of therapy/after enrollment were included. For group C, which had no start with ant-TNF therapy and/or IM, we selected the time point of enrolment for the start of the analysis.

Time-point for data export was 29 October 2018. Multiple variables were extracted from the SIBDCS database, which are listed in the Supplemental material. For the follow-up evaluation and measurements, annual follow-up questionnaires were analyzed. The reporting of this study conforms to the STROBE statement (see Supplemental material for Strobe Checklist for cohort studies).[27]

For each patient in group A or B, the start of the analysis (baseline) was determined by the day either immunomodulatory therapy and/or anti-TNF therapy treatment was first recorded in the SIBDC database. We used follow-up data up to 5 years later for the follow-up analyses. If, during follow up, the other medication (either immunomodulatory therapy or anti-TNF therapy) was started, the patient was considered a group B patient. Patients from groups A–C were excluded from the study if a treatment in group A and B or no treatment in group C were not consistently documented until the end of follow up. In three patients in group C, vedolizumab was started at the end of the observation period. No tofacitinib and no ustekinumab was used in our patients. Specifically, patients qualified for group C only if neither immunomodulatory therapy nor anti-TNF therapy treatment had been recorded during follow up. Intermittent local or systemic steroid treatment was not an exclusion criterion, but was accounted for in the multivariable model.

After an initial assessment at the study entry, symptoms of depression and anxiety were assessed at 1 year (180–540 days), 3 years (900–1599 days), and 5 years ($\geq$1600 days) after start of treatment (or enrollment in group C).

Psychometric measures

The hospital anxiety and depression scale (HADS) is a self-assessment scale to rate mood in outpatients.[28] Details of psychometric measures can be found in the Supplemental material.

Statistical analyses

The *p* values for group differences within variables were calculated using Mann–Whitney *U*, Kruskall–Wallis, Chi-squared test, or Fisher's exact test, respectively, where appropriate. A two-sided p value of < 0.05 was considered as statistically significant. For all statistical analyses, STATA was used.

For the multivariable analysis, we performed linear mixed model regression analyses. Our models distinguish time dependent effects in all patients, short-term ($\leq$2.5 years) and long-term ($>$2.5 years) effects according to therapy as well as patient specific trends for anxiety or depression at baseline and changes over time (random effects); details can be found in the Supplemental material.

Disease activity was measured by the Crohn's disease activity index (CDAI; stable disease CDAI $<$ 150 for CD) and the Modified Truelove and Witts activity index (MTWAI) for UC. For MTWAI we used 2 categories: active (MTWAI$\geq$3) and remission (MTWAI $<$ 3).[29] To allow using IBD activity measures (MTWAI for UC patients and CDAI for CD patients) in a single model, we used *Z*-Score transformed values of MTWAI and CDAI. MTWAI and CDAI values were *Z*-score transformed to allow using both parameters in the same figure.

Results

Clinical characteristics at diagnosis, at therapy start, or at enrollment

Figure 1 shows the flow of patient recruitment for this study. A total of 581 patients were included in our observational analysis (113 in group A, 193 in group B, 275 in group C). The main baseline characteristics are shown in Table 1. CD was more frequent in group B (anti-TNF therapy$\pm$ immunomodulatory therapy) than in group A

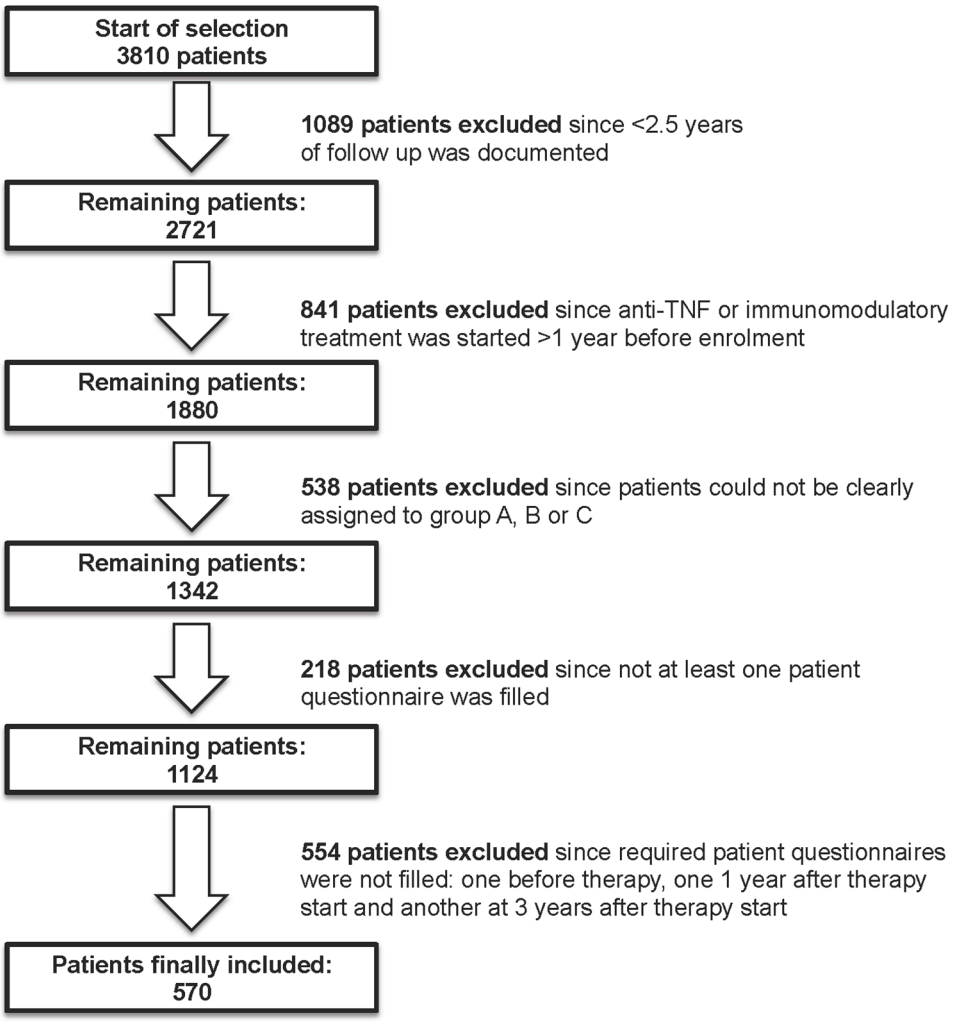

Figure 1. Flow chart of patient selection.

(immunomodulatory therapy) and least frequent in group C (control group). Further, patients in group B were younger at diagnosis and patients in group C were oldest at the start of observation (Table 1).

Most sociodemographic characteristics at baseline including education, smoking, break up of a relationship, and level of employment were distributed evenly between groups (Supplemental Table S1); however, absence from work was reported most frequently by patients in group B ($p < 0.001$). Within group B, absence from work was correlated significantly with increased depressive symptoms at 1 year after therapy start ($r = 0.15$), but not at the other three time points assessed. Absence from work showed no significant association with anxiety symptoms at any time point.

Levels of anxiety (HADS-A) were similar in all three groups (Table 2) but depressive symptoms before therapy were higher in group B ($p < 0.001$).

Clinical characteristics during follow up

Patients were followed for up to 5 years (Supplemental Table S3). Some patients in all groups experienced active disease (CDAI > 150, MTWAI ⩾ 3), with the lowest percentage of disease activity in group C and the highest percentage of disease activity in group A [66.9% *versus* 74.3%, non-significant (n.s.)] during follow up. Further, a considerable fraction of patients in all groups were treated with steroids. As expected, rates of steroid treatment were significantly higher in group A (60.2%) and groups B (62.2%)

Table 1. Baseline clinical characteristics of patient groups.

	Group A	Group B	Group C	Total	*p* value
Number of patients (%)	113 (19.5)	193 (33.2)	275 (47.3)	581 (100)	
Gender (%)					
Male	61 (54.0)	101 (52.3)	129 (46.9)	291 (50.1)	0.335
Female	52 (46.0)	92 (47.7)	146 (53.1)	290 (49.9)	
Initial diagnosis (%)					
Crohn	53 (46.9)	124 (64.2)	72 (26.2)	249 (42.9)	**<0.001**
UC/IBD unclassified	60 (53.1)	69 (35.8)	203 (73.8)	332 (57.1)	
Age at diagnosis					
Median, q25–q75, min–max	30.2, 21.5–41.1, 13.0–78.8	26.4, 19.2–38.8, 3.9–78.3	31.9, 24.7–41.4, 4.6–78.1	30.4, 21.9–40.6, 3.9–78.8	**0.002**
Age at therapy start (or at enrollment)					
Median, q25–q75, min–max	38.9, 29.0–51.3, 13.0–79.9	39.0, 26.6–48.9, 8.4–82.3	44.3, 36.0–56.7, 4.9–81.8	42.2, 31.2–53.0, 4.9–82.3	**<0.001**
Disease duration until therapy or enrollment					
Median, q25–q75, min–max	4.8, 1.2–11.7, 0.0–31.7	6.0, 2.1–13.3, 0.1–41.8	8.8, 2.3–18.2, 0.1–52.3	7.0, 2.0–15.2, 0.0–52.3	**0.001**
Initial CD location					
L1 (ileum) (%)	13 (24.5)	26 (23.2)	20 (30.8)	59 (25.6)	0.58
L2 (colon) (%)	11 (20.8)	21 (18.7)	16 (24.6)	48 (20.9)	
L3 (ileum and colon) (%)	27 (50.9)	62 (55.4)	29 (44.6)	118 (50.3)	
L4 (upper GI only) (%)	2 (3.8)	3 (2.7)	0 (0.0)	5 (2.2)	
Missing or unknown	*0*	*12*	*7*	*19*	
Initial UC location					
Proctitis (%)	8 (13.6)	11 (18.3)	70 (38.5)	89 (29.6)	**<0.001**
Left-sided colitis (%)	21 (35.6)	21 (35.0)	63 (34.6)	105 (34.9)	
Pancolitis (%)	30 (50.8)	28 (46.7)	49 (26.9)	107 (35.5)	
Missing or unknown	*1*	*9*	*21*	*31*	

Values reflect absolute numbers with percentage in parentheses.
Bold entries indicate statistical significance.
GI, gastrointestinal; IBD, inflammatory bowel diseases; UC, ulcerative colitis.

compared with groups C (26.5%, $p < 0.001$) with more severe disease and more disease exacerbations in patients of group A and B. A substantial fraction of patients also experienced extra intestinal manifestation (EIM), complications, perianal fistula and/or abscess or stenosis, or surgery with the lowest morbidity in group B ($p < 0.001$).

Table 2. Psychiatric morbidity of patients at baseline and during follow up. Anxiety is shown as HADS-A, depressive symptoms as HADS-D scores.

	Group A	Group B	Group C	Total	*p* value
Number of patients (%)	113 (19.5)	193 (33.2)	275 (47.3)	581 (100)	
Rates of 5-ASA ANXIETY (%)	90 (79.6)	147 (76.2)	248 (90.2)	485 (83.5)	**<0.001**
Before therapy					
Median, q25–q75, min–max, *n*	5.5, 3–8.5, 0–20, *n* = 112	6, 3–9, 0–18, *n* = 177	5, 3–8, 0–19, *n* = 266	5, 3–8, 0–20, *n* = 555	0.276
After 1 year					
Median, q25–q75, min–max, *n*	5, 3–8, 0–17, *n* = 109	5, 2–7, 0–18, *n* = 170	5, 2–7, 0–20, *n* = 260	5, 3–7, 0–20, *n* = 539	0.242
After 3 years					
Median, q25–q75, min–max, *n*	5, 2.3–8, 0–17, *n* = 94	5, 3–8, 0–16, *n* = 123	5, 2–8, 0–16, *n* = 216	5, 3–8, 0–17, *n* = 433	0.753
After 5 years					
Median, q25–q75, min–max, *n*	4, 2–7, 0–18, *n* = 63	5, 3–9, 0–19, *n* = 90	5, 2–7, 0–18, *n* = 150	5, 2–8, 0–19, *n* = 303	0.312
p value before *versus* 1 years	0.775	**0.032**	0.252	**0.032**	
p value before *versus* 3 years	0.197	0.277	0.509	0.092	
p value before *versus* 5 years	0.224	0.663	0.222	0.091	
Depression					
Before therapy					
Median, q25–q75, min–max, *n*	3.5, 1–7, 0–17, *n* = 112	4, 1–7, 0–15, *n* = 177	2, 1–4, 0–17, *n* = 266	3, 1–6, 0–17, *n* = 555	**<0.001**
After 1 year					
Median, q25–q75, min–max, *n*	2, 1–6, 0–17, *n* = 109	2, 1–6, 0–16, *n* = 170	2, 0–4.3, 0–18, *n* = 260	2, 0–5, 0–18. *n* = 539	0.097
After 3 years					
Median, q25–q75, min–max, *n*	2, 0–6, 0–18, *n* = 94	3, 1–6, 0–15, *n* = 123	2, 0.5–4, 0–17, *n* = 216	2, 1–5, 0–18, *n* = 433	0.062
After 5 years					
Median, q25–q75, min–max, *n*	2, 1–5, 0–20, *n* = 63	3, 1–7, 0–17, *n* = 89	1, 0–5, 0–20, *n* = 150	2, 0–5, 0–20, *n* = 302	0.075
p value before *versus* 1 year	**0.039**	**0.005**	0.347	**0.001**	
p value before *versus* 3 years	0.068	0.052	0.529	**0.011**	
p value before *versus* 5 years	0.051	0.182	0.275	**0.012**	

Values reflect median with IQR.
Bold entries indicate statistical significance.
5-ASA, 5-aminosalicylate; HADS, hospital anxiety and depression scale ; IQR, interquartile range.

Table 3. Linear mixed model for treatment effects on anxiety and depressive symptoms. Values reflect regression coefficient B with 95% CI.

	Linear mixed model for anxiety	Linear mixed model for depression
	Coefficient (95% CI; *p* value)	
Fixed effects		
Intercept (β_0)	5.437 (5.012–5.862; <**0.001**)	2.961 (2.577–3.345; <**0.001**)
z-score of initial disease activity	0.297 (0.048–0.546; **0.019**)	0.563 (0.332–0.794; <**0.001**)
Time (β_1)	−0.066 (−0.147 to 0.015; 0.108)	0.001 (−0.078 to 0.078; 0.998)
Short-term[a] time effect after imm.-mod. therapy ($\beta_1 + \beta_2$)	−0.291 (−0.789 to 0.208; 0.253)	−0.664 (−1.132 to −0.196; **0.005**)
Long-term[a] time effect after imm.-mod. therapy ($\beta_1 + \beta_3$)	−0.148 (−0.284 to −0.013; **0.032**)	−0.147 (−0.278 to −0.017; **0.027**)
Short-term[a] time effect after anti-TNF therapy ($\beta_1 + \beta_4$)	−0.712 (−1.147 to −0.277; **0.001**)	−0.737 (−1.146 to −0.329; <**0.001**)
Long-term[a] time effect after anti-TNF therapy ($\beta_1 + \beta_5$)	−0.132 (−0.242 to −0.022; **0.018**)	−0.127 (−0.233 to −0.020; **0.020**)
Being in Group A (β_6)	0.504 (−0.337 to 1.345; 0.240)	1.060 (0.300–1.820; **0.006**)
Being in Group B (β_7)	0.452 (−0.272 to 1.176; 0.221)	1.077 (0.424–1.731; **0.001**)
Random effects		
SD for the intercept [[[IMG]]10.1177_17562848211033763-ineq1.eps[[/IMG]]	3.098 (2.868–3.347)	2.759 (2.547–2.988)
SD for the slope [[[IMG]]10.1177_17562848211033763-ineq2.eps[[/IMG]]]	0.224 (0.129–0.389)	0.241 (0.158–0.370)
Correlation between X and Y	−0.095 (−0.366 to 0.192)	0.184 (−0.144 to 0.476)

[a]Short-term (⩽2.5 years) and long-term effects (>2.5 years) according to therapy.
Bold entries indicate statistical significance.
CI, confidence interval; imm.-mod., immuno-modulatory; SD, standard deviation; TNF tumor necrosis factor.

Anxiety and depressive symptoms tended to decrease in all patient groups over the 5-year observation period (Table 2, Supplemental Figure S1); a significant improvement was seen at 1-year follow up in group B for anxiety and depression and in group A for depressive symptoms.

Multivariable model to capture effects of treatment on anxiety and depressive symptoms

To identify potential time-dependent effects of treatment in our heterogeneous patient population, a mixed effects model was built, accounting for short-term and long-term effects of treatment as well as individual patient baseline values for anxiety and depressive symptoms and individual trends in patients. Two separate models, for anxiety and depression, respectively, were built, with and without adjustment for potential confounders (Table 3, Figure 2).

Within the first 2.5 years after start of therapy, Group B (anti-TNF therapy ± immuno-modulatory therapy) was associated with an improvement of symptoms (anxiety: improvement of HADS-A by 0.712 points per year, $p = 0.001$; depressive

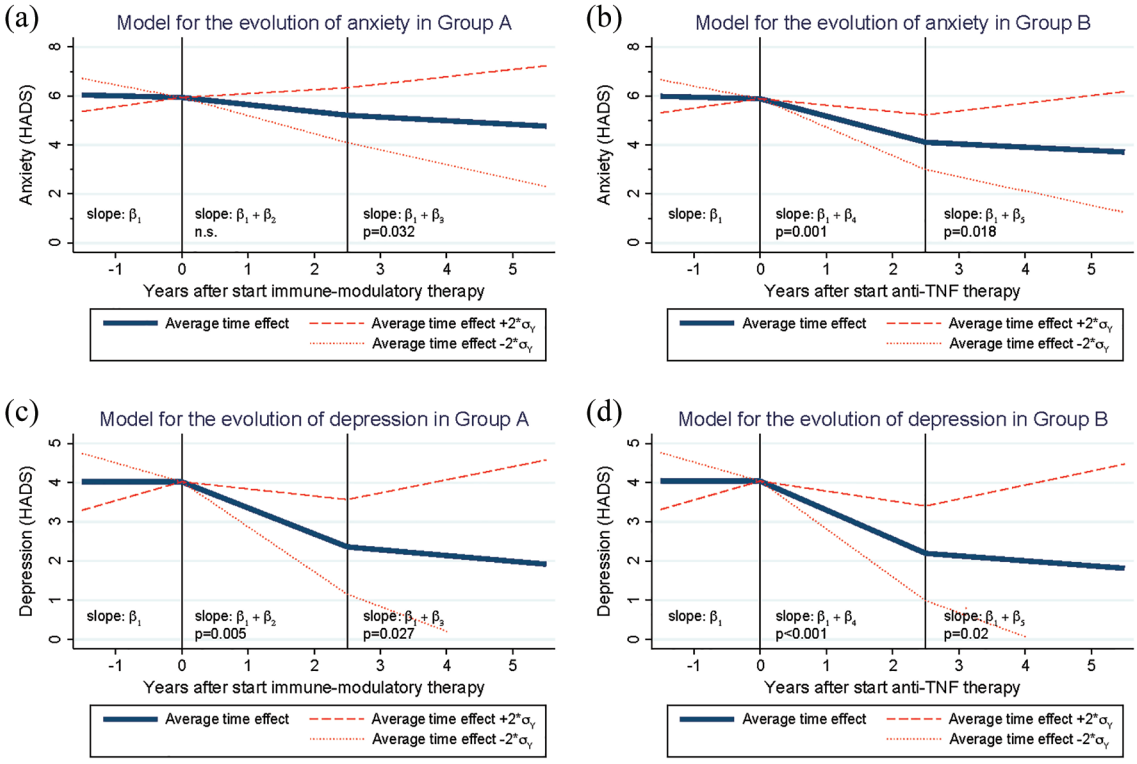

Figure 2. Trends for anxiety and depressive symptoms over time in a mixed model. Our mixed model distinguishes the first 2.5 years after start of therapy and the time following it. The blue line indicates the average evolution of depression. Red lines indicate the margins of error: trajectories of patients will be situated in the zone between red lines with a statistical probability of 95%. (a) Model of evolution of anxiety in Group A; (b) Model of evolution of anxiety in Group B; (c) Model of evolution of depressive symptoms in Group A; (d) Model of evolution of depressive symptoms in Group B.
HADS, hospital anxiety and depression scale; TNF, tumor necrosis factor.

symptoms: improvement of HADS-D by 0.737 points per year, $p < 0.001$). After 2.5 years, psychiatric symptoms continued to improve significantly, even though at a lower rate (anxiety: 0.132 points improvement per year, $p = 0.018$; depressive symptoms: 0.127 improvement per year, $p = 0.020$). For immunomodulatory therapy, similar trends were observed, although anxiety improved significantly only after 2.5 years. The magnitude of a significant improvement was similar in group A and B (Table 3, Figure 2).

Corrected multivariable model to capture effects of treatment on anxiety and depressive symptoms

To assess robustness of our findings, we included potential confounders in our model (Table 4), correcting for age, disease duration, diagnosis, steroid intake, complications, EIM, surgery, fistula, stenosis, smoking, absence from work, education level, and stressful life events (break-up in a relationship). Even after correction for confounders, effects of treatment on anxiety and depressive symptoms remained robust with a treatment-related improvement in both anxiety and depressive symptoms within the first 2.5 years and also after 2.5 years in group B. Similarly, for group A, correcting for confounders yielded long-term improvement of anxiety and both short-term and long-term improvement in depressive symptoms.

Depressive symptoms also significantly improved in patients working during follow up and, additionally, in those with fistula/abscess.

Multivariable model to capture effects of treatment on disease activity

Parallel to improvements in depressive symptoms and anxiety, treatment with either anti-TNF therapy or immunomodulators reduced disease activity within the first year and after 2.5 years, with weaker effects beyond 2.5 years. For disease

Table 4. Linear mixed model for treatment effects on anxiety and depressive symptoms, corrected for confounders. Values reflect regression coefficient B with 95% CI.

	Linear mixed model for anxiety with confounders	Linear mixed model for depressive symptoms with confounders
	Coefficient (95% CI; *p* value)	
Fixed effects		
Intercept (β_0)	6.265 (4.411–8.119; <**0.001**)	4.322 (2.618–6.025; <**0.001**)
z-score of initial disease activity	0.285 (0.009–0.560; **0.043**)	0.481 (0.227–0.734; <**0.001**)
Time (β_1)	−0.080 (−0.162 to 0.002; 0.056)	−0.012 (−0.091 to 0.068; 0.771)
Short-term[a] time effect after imm.-mod. therapy ($\beta_1 + \beta_2$)	−0.264 (−0.766 to 0.238; 0.303)	−0.680 (−1.154 to −0.206; **0.005**)
Long-term[a] time effect after imm.-mod. therapy ($\beta_1 + \beta_3$)	−0.158 (−0.296 to −0.020; **0.025**)	−0.153 (−0.286 to −0.019; **0.025**)
Short-term[a] time effect after anti-TNF therapy ($\beta_1 + \beta_4$)	−0.825 (−1.274 to −0.375; <**0.001**)	−0.826 (−1.251 to −0.401; <**0.001**)
Long-term[a] time effect after anti-TNF therapy ($\beta_1 + \beta_5$)	−0.128 (−0.241 to −0.016; **0.026**)	−0.131 (−0.241 to −0.022; **0.019**)
Being in Group A (β_6)	0.644 (−0.266 to 1.553; 0.166)	1.226 (0.402–2.050; **0.004**)
Being in Group B (β_7)	0.447 (−0.403 to 1.297; 0.303)	1.031 (0.260–1.802; **0.009**)
Gender: female (male 0 = ref)	1.065 (0.487–1.643; <**0.001**)	0.133 (−0.399 to 0.665; 0.624)
Age	−0.024 (−0.049 to 0.002; 0.067)	0.001 (−0.023 to 0.024; 0.977)
Disease duration	0.001 (−0.033 to 0.035; 0.950)	0.006 (−0.025 to 0.037; 0.709)
Initial diagnosis (ref: CD)	0.139 (−0.593 to 0.872; 0.709)	−0.509 (−1.183 to 0.165; 0.139)
Steroid intake during therapy or follow up (ref: no)	−0.386 (−1.001 to 0.229; 0.219)	0.025 (−0.541 to 0.591; 0.931)
Complication during therapy or follow up	−0.160 (−0.784 to 0.463; 0.614)	0.081 (−0.493 to 0.655; 0.782)
EIM during therapy or follow up	0.771 (0.179–1.363; **0.011**)	0.413 (−0.132 to 0.958; 0.138)
Surgery during therapy or follow-up	0.473 (−0.259 to 1.206; 0.205)	0.612 (−0.062 to 1.286; 0.075)
Fistula/abscess during therapy or follow up	−0.624 (−1.429 to 0.181; 0.129)	−0.929 (−1.671 to −0.187; **0.014**)
Stenosis during therapy or follow up	−0.186 (−1.033 to 0.661; 0.666)	−0.589 (−1.369 to 0.190; 0.138)
Used to smoke during therapy or follow up	0.694 (0.064–1.323; **0.031**)	0.300 (−0.279 to 0.880; 0.310)
Worker during therapy or follow up	−1.043 (−1.920 to −0.165; **0.020**)	−1.820 (−2.628 to −1.012; <**0.001**)

(Continued)

Table 4. (Continued)

	Linear mixed model for anxiety with confounders	Linear mixed model for depressive symptoms with confounders
	Coefficient (95% CI; *p* value)	
Absent from work at least once during therapy or follow up	0.316 (–0.373 to 1.005; 0.368)	0.573 (–0.060 to 1.207; 0.076)
Educational level: low	0 (ref)	0 (ref.)
Educational level: middle	–0.283 (–1.036 to 0.470; 0.462)	–0.605 (–1.298 to 0.088; 0.087)
Educational level: high	–0.028 (–0.674 to 0.618; 0.932)	0.076 (–0.519 to 0.670; 0.803)
Break-up during therapy or follow-up	0.425 (–0.511 to 1.360; 0.374)	–0.255 (–1.117 to 0.606; 0.561)
Random effects		
SD for the intercept [[[IMG]]10.1177_17562848211033763-ineq3.eps[[/IMG]]	2.998 (2.766–3.249)	2.656 (2.444–2.887)
SD for the slope [[[IMG]]10.1177_17562848211033763-ineq4.eps[[/IMG]]]	0.234 (0.141–0.389)	0.250 (0.167–0.374)
Correlation between X and Y	–0.141 (–0.401 to 0.140)	0.077 (–0.220 to 0.361)

[a]Short-term (⩽2.5 years) and long-term (>2.5 years) effects according to therapy.
Bold entries indicate statistical significance.
CD, Crohn's disease; CI, confidence interval; EIM, extra intestinal manifestation; SD, standard deviation.

activity, improvements in group A and group B were similar (Supplemental Figure S2, Supplemental Table S2).

Discussion

We found a significant decrease in depression in patients treated with TNF inhibitors or immune modulators compared with no therapy during the first 2.5 years of treatment. TNF inhibitor treatment was also associated with an improvement in anxiety within the first 2.5 years. Both depression and anxiety continued to improve beyond 2.5 years, but at lower rates. Symptoms of anxiety and depression tended to decrease in all patient groups and a significant improvement was seen at the 1-year follow-up in group B for anxiety and depressive symptoms and in group A for depressive symptoms. To our knowledge, this is the first longitudinal analysis on the course of anxiety and depressive symptoms across several time points in a large sample of an IBD cohort. Our findings are in line with results from a previously published smaller observational study Lix *et al.*[30]

The frequency of psychiatric conditions is increased in patients with IBD with a reported prevalence of depression and anxiety of 21–31% and 26–30%, respectively.[17,31,32] In active IBD, psychiatric symptoms are more prevalent than in quiescent disease.[32] Therefore, it is important to understand whether IBD treatment with TNF-inhibitors or immune modulators will improve or worsen pre-existing anxiety or depression in IBD patients. Detection of significant effects required a linear mixed effects models regression analysis accounting for group differences and random effects. Of note, these differences did not reach significance in our direct group comparison (Table 2), most likely due to the high variance.

Baseline disease parameters differed between treatment groups and factors like a diagnosis of CD, disease location and extend of disease, as well longer disease duration, previous surgeries, fistulas,

or EIM were associated with higher use of anti-TNF therapy or immunomodulatory therapy. However, anti-TNF therapy and/or immunomodulatory therapy remained robust predictors for patients' mood in a corrected multivariable analysis considering sociodemographic variables and IBD-specific variables, including therapy with corticosteroids, which was allowed in every group (Table 4). Therefore, our combined analysis suggests an association of anti-TNF therapy and immunomodulatory therapy with improvements in mood. But we could not distinguish if anti-TNF would have a direct or indirect effect on changes in mood.

There are only few studies to date investigating the effect of anti-TNF treatment and immunomodulatory therapy on mood in patients with IBD. As in our study, all previous studies are observational in nature. Choi *et al.* performed a nation-wide population based cohort study in South Korea and followed 15,569 IBD patients and 46,707 controls over a mean of 6 years and observed a HR of 1.6 due to IBD for the onset of anxiety and a HR of 2 for depressive symptoms, respectively.[9] However, therapy with anti-TNF or immunomodulatory treatment protected patients from both conditions.[9] In another cross-sectional analysis with 120 IBD patients, individuals with depressive symptoms were more likely to have active disease; however, use of anti-TNF therapy was negatively associated with depressive symptoms (11.5% anti-TNF-treatment in depressed patients *versus* 42.3% without depressive symptoms[33]). In another observational study with 160 IBD patients with moderate-to-severe disease, resolution of anxiety and depressive symptoms at week 6 after start of treatment was similar upon treatment with anti-TNFs and vedolizumab.[34]

Overall, these results, as well as our data, confirm that effective anti-inflammatory treatment is able to treat both bowel inflammation and psychiatric symptoms. However, it should be noted that, in rare cases, depressive symptoms and even suicidal behavior has been associated with anti-TNF therapy.[35]

The SIBDCS did not systematically assess circulating inflammatory markers like C-reactive protein (CRP) and TNF. Therefore, we could not test whether systemic inflammation can induce depressive symptoms as previously suggested for inflammatory somatic diseases,[36] including IBD.[37] In line with these observations, in CD patients, depressive symptoms were associated with different cytokine profiles and macrophage differentiation patterns.[38] Another, albeit related, theory posits that inflammation triggers sickness behavior that is characterized not only by depression-like behaviors but also anxiety,[39] wherein TNF may play a paramount role.[40] Therefore, a gut–brain axis might impact on the outcome of anxiety and depressive symptoms in IBD patients.[41]

Strengths of our study include a sample size of more than 570 patients and the longitudinal design with a follow-up time of several years with sequential HADS measurements. Further, our multivariable analysis accounts for a range of potentially important confounding variables. One limitation is our lack of information about the duration of active disease phases and the cumulative exposure to inflammation. Another limitation is a potential selection bias for higher anxiety and depressive symptom scores due to a higher proportion of UC/IBD unclassified and proctitis in the group receiving neither anti-TNF therapy nor IM compared with the other two treatment groups. Moreover, exact dosages of anti-TNFs and immunomodulatory therapy and trough or drug levels are unknown. In addition, patient's compliance could not be assessed reliably due to a lack of information regarding drug prescriptions and dispensing, a common shortcoming of cohort studies. Regarding steroid treatment the SIBDC data base lacks specific information on tapered dosages and cumulative dosages over time. Therefore, and as a limitation, rates of "steroid treatment" (i.e., any usage of peroral or intravenous steroids) is the best surrogate we can provide. The absence of a quantitative variable for steroid use and other covariates, as well as the lack of time-dependent variables, are further limitations of our study. Furthermore, we cannot exclude the possibility that, in group B, combined therapy with anti-TNF therapy with immunomodulatory therapy had a different effect than anti-TNF treatment alone. Instead of a clinical interview, anxiety and depressive symptoms were assessed with a self-rated instrument. Regarding the mechanism of improvements in depressive symptoms, our study does not distinguish direct effects of anti-TNF therapy on mood from indirect effects on mood *via* treatment of the underlying IBD. However, our models have been corrected for disease activity. This means that the observed effects were present even after the correction for the fact that some patients in group

A and B did not reach a remission, whereas others in these groups did. Unfortunately, a dedicated subanalysis limited to patients with clear remission and patients with persistent inflammation over several years was not possible since only a minority of patients would have been eligible for such a subgroup analysis. Lastly, our results are based on longitudinal observations and cannot claim causality for effects of anti-TNF treatment and/or immunomodulatory therapy on mood. For this, in future randomized controlled trials, anxiety and depressive symptoms should be consistently addressed as secondary outcomes.

Taken together, anti-TNF treatment and immunomodulatory therapy affect patient's mood with strongest improvement seen within the first 2.5 years of therapy. Therefore, in case of active IBD the responsible physician should also inquire about anxiety and/or depressive symptoms, since efficient IBD treatment might improve both gastrointestinal and psychiatric symptoms. Our study does not allow a statement as to whether the improvement in mood occurred directly *via* medication effects on inflammation-driven neurobehavioral processes or indirectly *via* a reduction in disease activity.[6,42] Moreover, in future randomized controlled trials for IBD treatment, mood should consistently be considered as secondary outcome.

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Author contributions

Concept and design: ARS, BM, RvK. Acquisition, analysis or interpretation of the data: ARS, BM, RvK, PS, MB, TK, NK, SJ, LB, GR. Drafting of the manuscript: ARS, BM, RvK, PS, MB, TK, NK, SBUJ, LB, GR. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: JBR. Supervision of statistical analysis: ARS, BM, RvK.

Conflict of interest statement

ARS has served on an advisory board and received consulting honoraria from AMGEN, Bayer, BMS, IPSEN, Lilly, Merck, Pfizer, Sanofi, and Servier for work performed outside the current study. BM has served on an advisory board for Gilead und Novigenix, has received traveling fees or speaking fees from given Imaging, MSD, Vifor, Takeda, and Novartis, and has received an unrestricted research grant from MSD, outside of the submitted work. GR has consulted to Abbvie, Augurix, BMS, Boehringer, Calypso, Celgene, FALK, Ferring, Fisher, Genentech, Gilead, Janssen, MSD, Novartis, Pfizer, Phadia, Roche, UCB, Takeda, Tillots, Vifor, Vital Solutions, and Zeller; GR has received speaker's honoraria from Astra Zeneca, Abbvie, FALK, Janssen, MSD, Pfizer, Phadia, Takeda, Tillots, UCB, Vifor, and Zeller; GR has received educational grants and research grants from Abbvie, Ardeypharm, Augurix, Calypso, FALK, Flamentera, MSD, Novartis, Pfizer, Roche, Takeda, Tillots, UCB and Zeller, for work performed outside the current study. JBR has nothing to disclose. LB reports grants from the Swiss National Science Foundation, during the conduct of the study; travel grants from Abbvie, MSD, Vifor, personal fees for consulting and advisory board work from Abbvie, Ferring, MSD, Pfizer, Shire, Takeda, UCB, Janssen, and a research grant from ThermoFisher, outside the submitted work. MB has nothing to disclose. NK has nothing to disclose.

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Trial registration

This study was a SIBDCS population-based analysis. No trial registration was necessary.

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Data availability statement

All data are incorporated into the article and its online Supplemental Material.

Supplemental material

Supplemental Material for this article is available online.

Ethics statement

The SIBDCS is funded by the Swiss National Science Foundation and has been approved by the local ethics committee of each participating center (institutional review board approval No. EK-1316 approved on 5 February 2007 and BASEC 2018-02068, approved on 9 March 2020). All patients provided written informed consent prior to inclusion into the SIBDCS.

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